TREATING C. DIFF IN 2019

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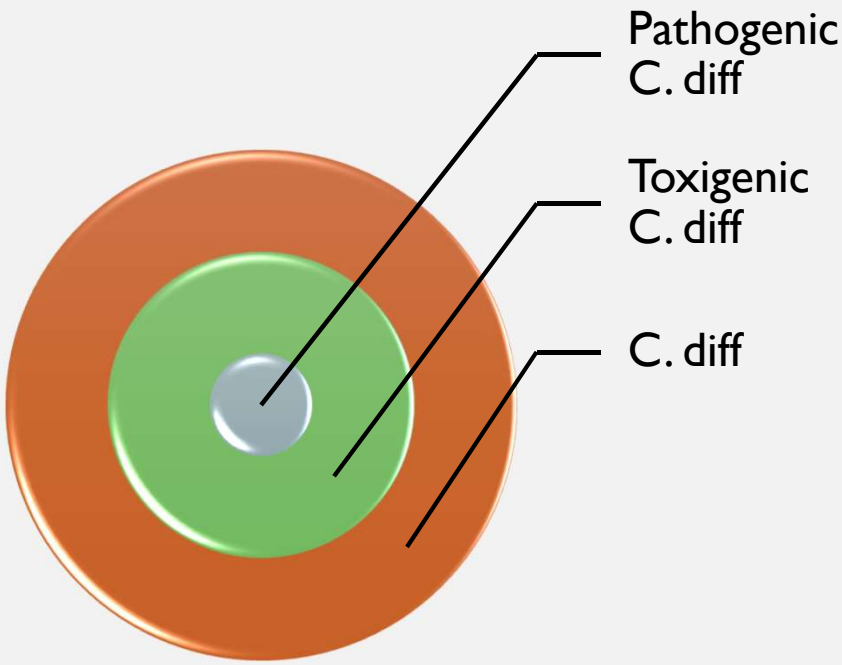
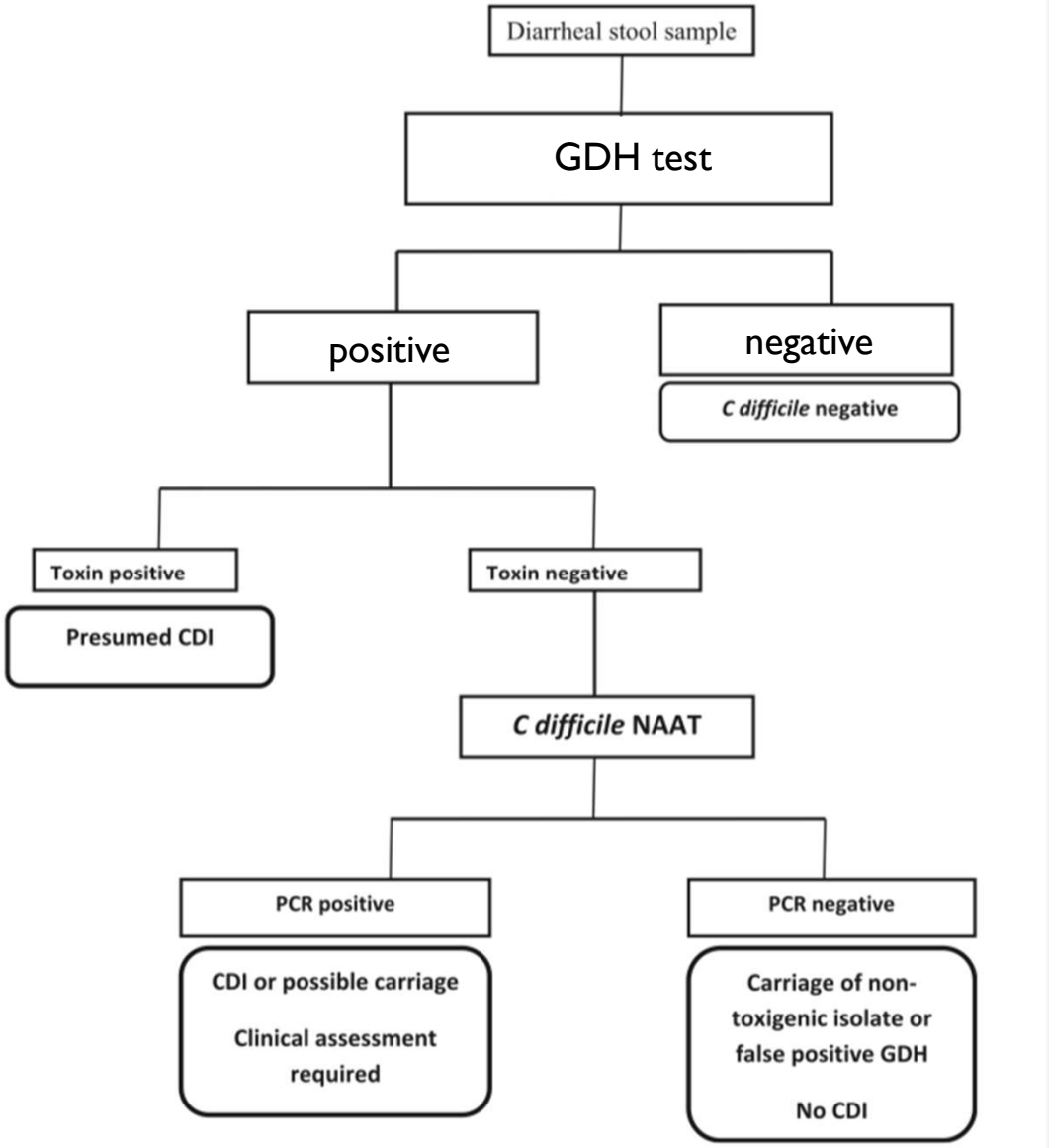
DIAGNOSING C. DIFF CORRECTLY



DIAGNOSING C. DIFF CORRECTLY

- To diagnose the presence of the organism → *glutamate dehydrogenase* (GDH)
  - > 90%-95% sensitive and specific – high negative predictive value
  - Low cost
- To diagnose the presence of pathogenic toxigenic C. diff → ELISA to toxins
  - Only ~70% sensitive, though very specific
  - A positive result is helpful, but a negative result isn't.
- To diagnose the presence of toxigenic C. diff → NAAT
  - Very sensitive
  - Can't distinguish CDI vs carriage of toxigenic C. diff

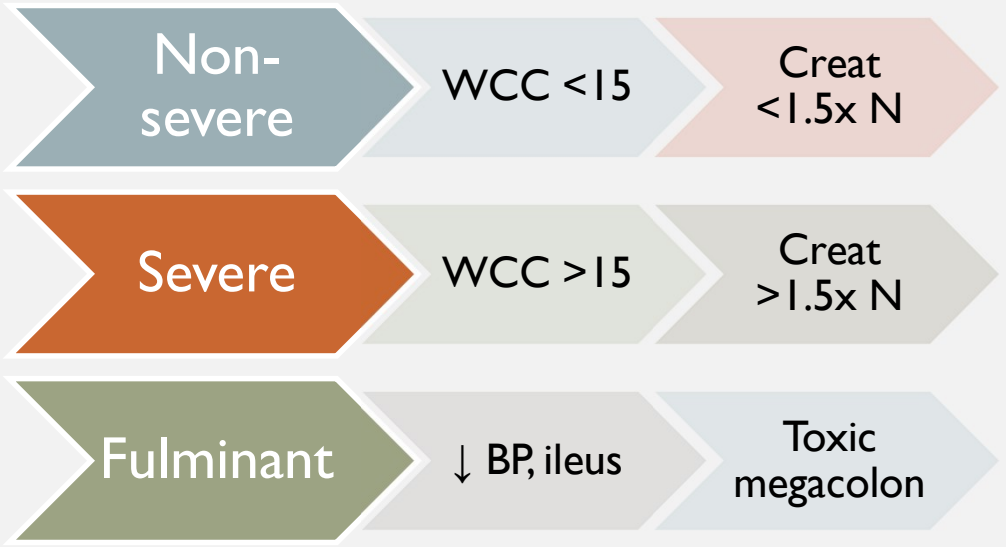


Anaerobe. 2011 Aug;17(4):170-4

REMEMBER:

- Only send diarrhoeal stools (≥3/24 hours, conform to the shape of the container!)
  - Exception = ileus
- No role for repeat testing within 7 days.
- No role for "test of cure" after treating.

TREATMENT OPTIONS



TREATMENT: NON-SEVERE

Traditionally:

- Metronidazole (Flagyl) 500mg 8-hourly PO

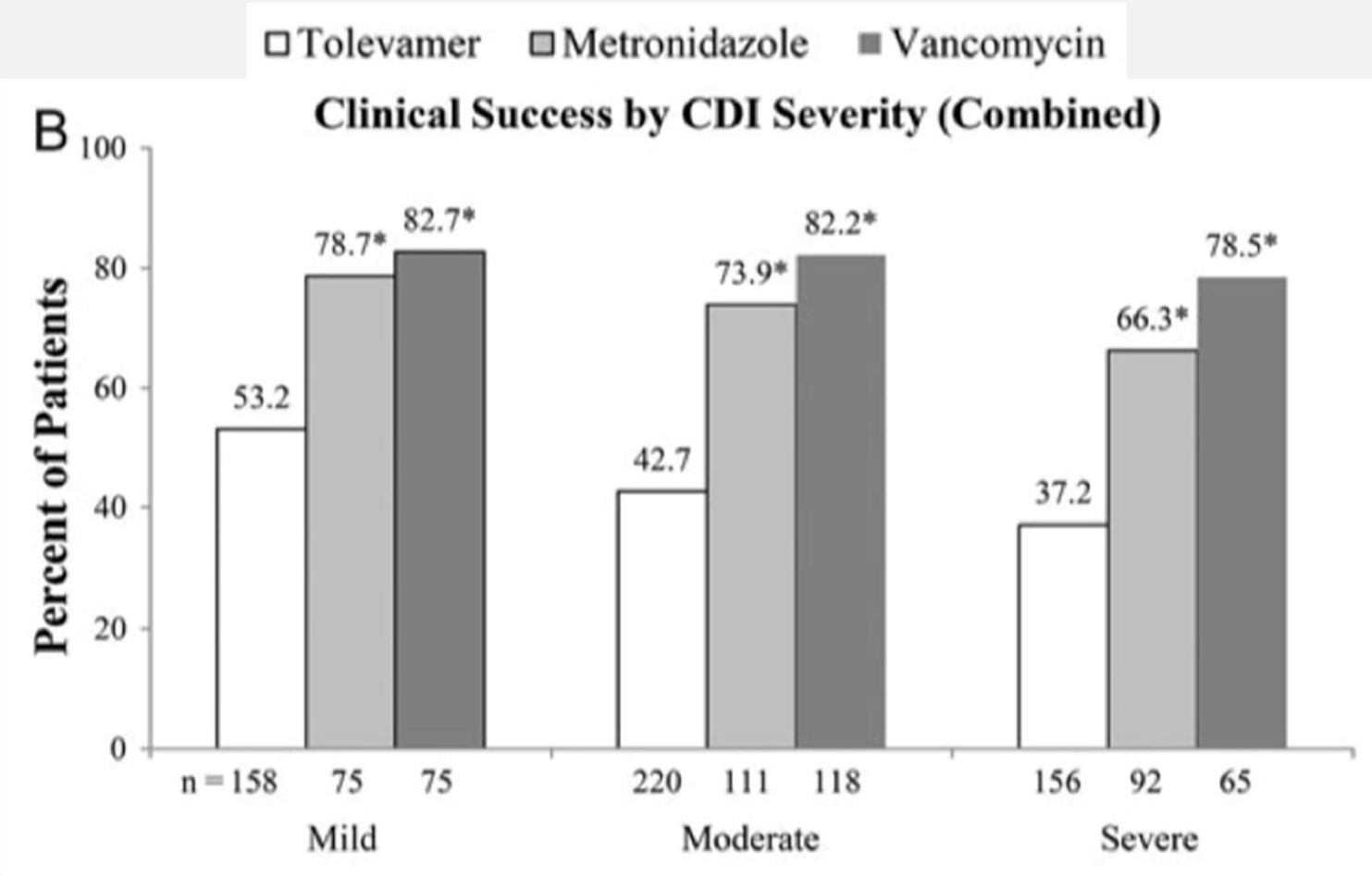
Alternatives:

- Vancomycin 125 mg 6-hourly PO
- Fidaxomicin 200mg 12-hourly PO

Duration: 10-14 days

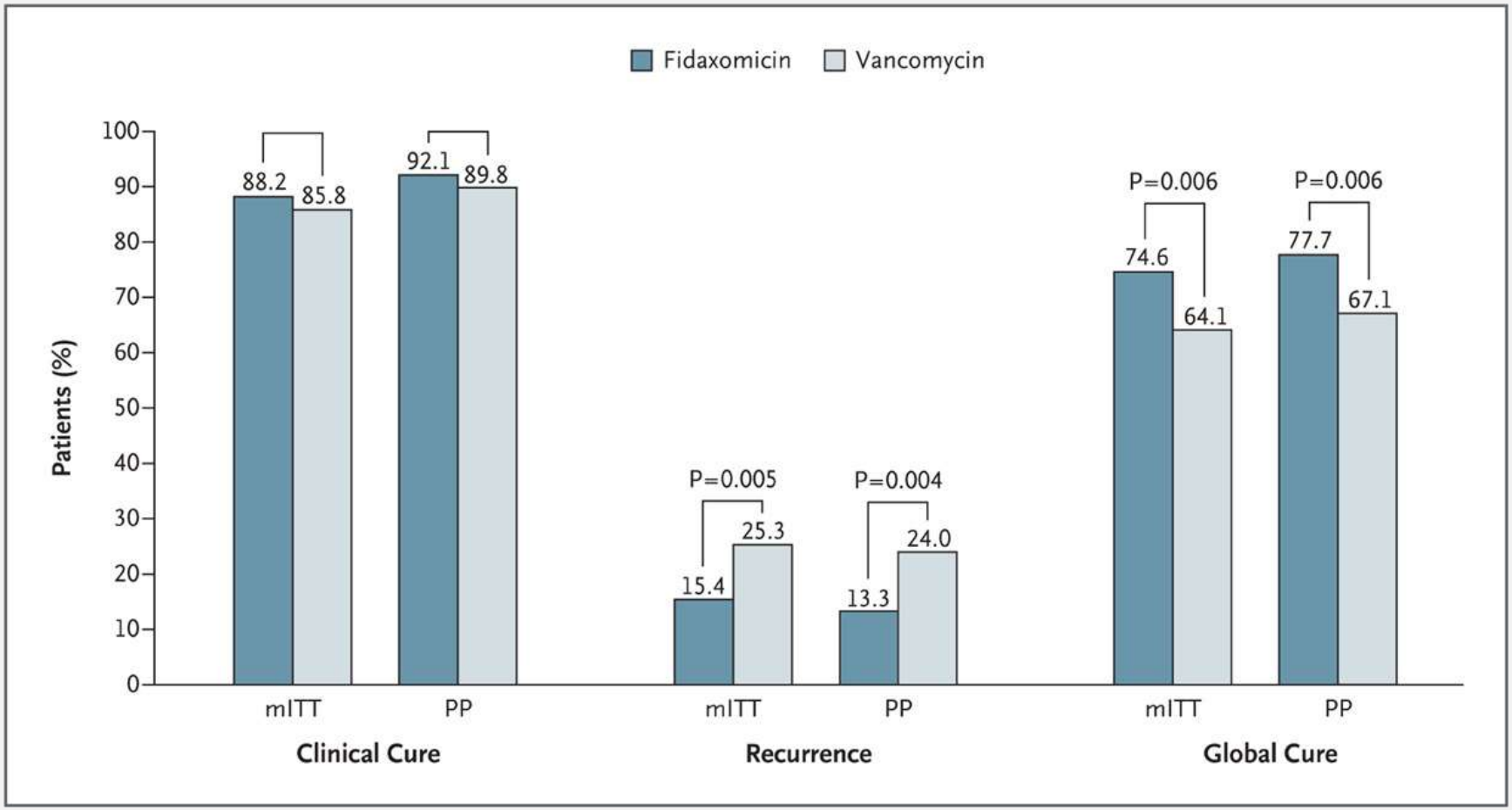
VANCOMYCIN VS METRONIDAZOLE

CID, 2014;
59(3): 345–354



FIDAXOMICIN VS VANCOMYCIN

N Engl J Med 2011; 364:422-431



TREATMENT: SEVERE

- Vancomycin 125 mg 6-hourly PO

  or

- Fidaxomicin 200mg 12-hourly PO

- Duration: 10-14 days

TREATMENT: FULMINANT

- Vancomycin 500 mg 6-hourly PO or via NGT
- If ileus:
  - Metronidazole 500mg q8 IVI, *AND*
  - Vancomycin rectally
- Consider surgical management:
  - Subtotal colectomy with rectum preservation
  - Diverting loop ileostomy (preserves colon & allows vancomycin colonic lavage – better outcomes?)

REMEMBER

- VANCOMYCIN DOESN'T CROSS THE GUT WALL (in either direction):
  - IV vancomycin has no effect on C. diff (may increase risk of it though!)
  - PO vancomycin is only used to treat C. diff
  - (Metronidazole is the opposite)

- STOP ALL OTHER ANTIBIOTICS (if at all possible)

RELAPSES

NATURAL HISTORY WITHOUT FMT

1. N Engl J Med 2006; 354:2200–15
2. Clin Infect Dis 2005; 40:1591–7
3. Am J Gastroenterol. 2002;97:1769-75
4. J Infect Dis. 2008; 197:435-8

FIRST RELAPSE

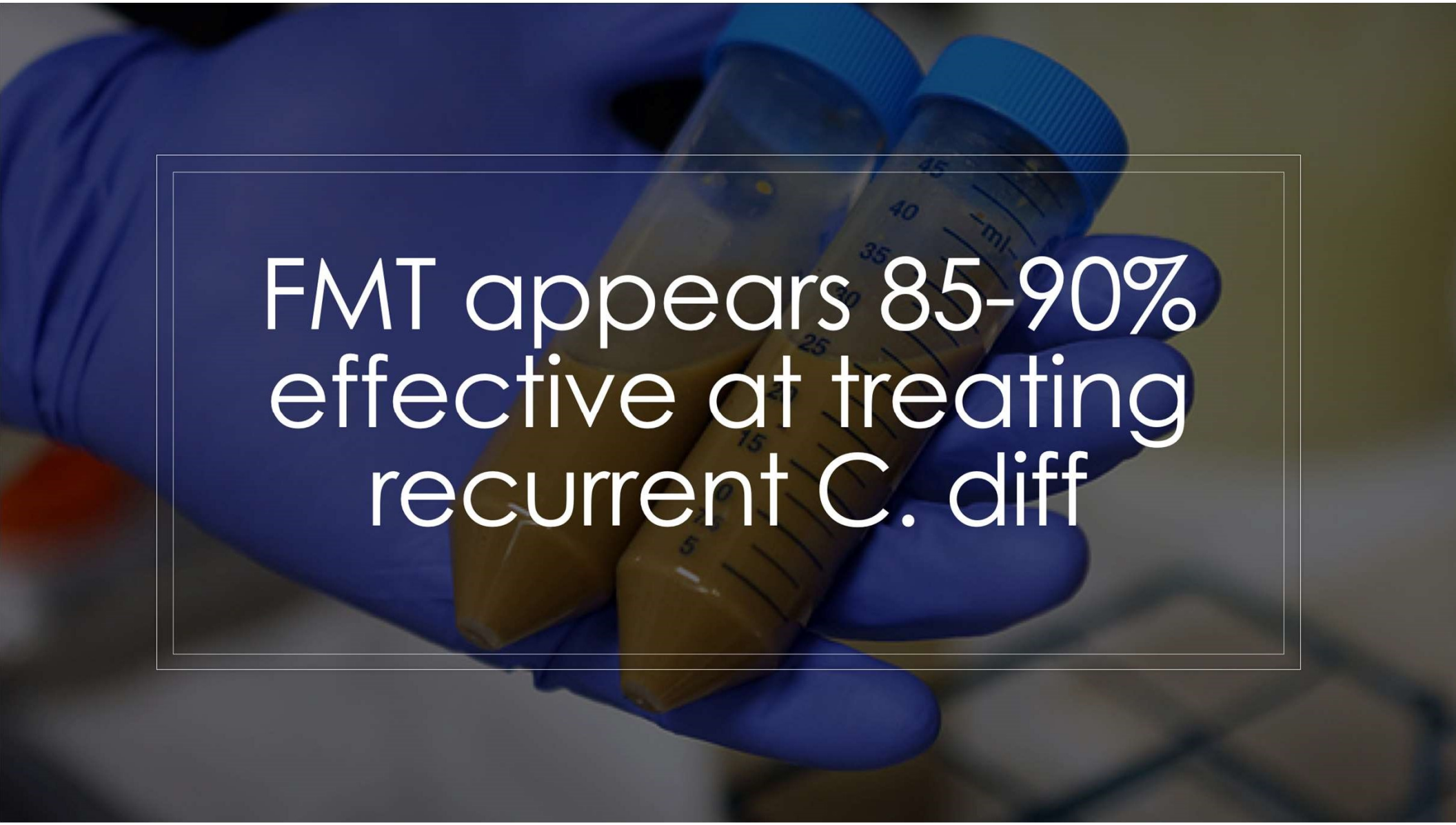
- If metronidazole used initially → use vancomycin.
- If vancomycin used initially → either:
  1. Fidaxomycin, or
  2. Vancomycin taper:
     - 125 mg 6-hourly PO x10 days, then
     - 125 mg 12-hourly PO x7 days, then
     - 125 mg daily PO x7 days, then
     - 125 mg every 2-3 days x2-6 weeks

≥SECOND RELAPSE

- Either try one of the previous relapse regimens again,

OR

- **Faecal microbiota transplantation (FMT)**


FMT appears 85-90% effective at treating recurrent C. diff

WHICH PATIENTS?

FMT is still an unlicensed med without good long-term follow up

Patients with ≥2 recurrences

These are risk factors for recurrences

1 relapse that was severe or complicated

"Refractory" disease

Low quality evidence: 2 studies with different definitions

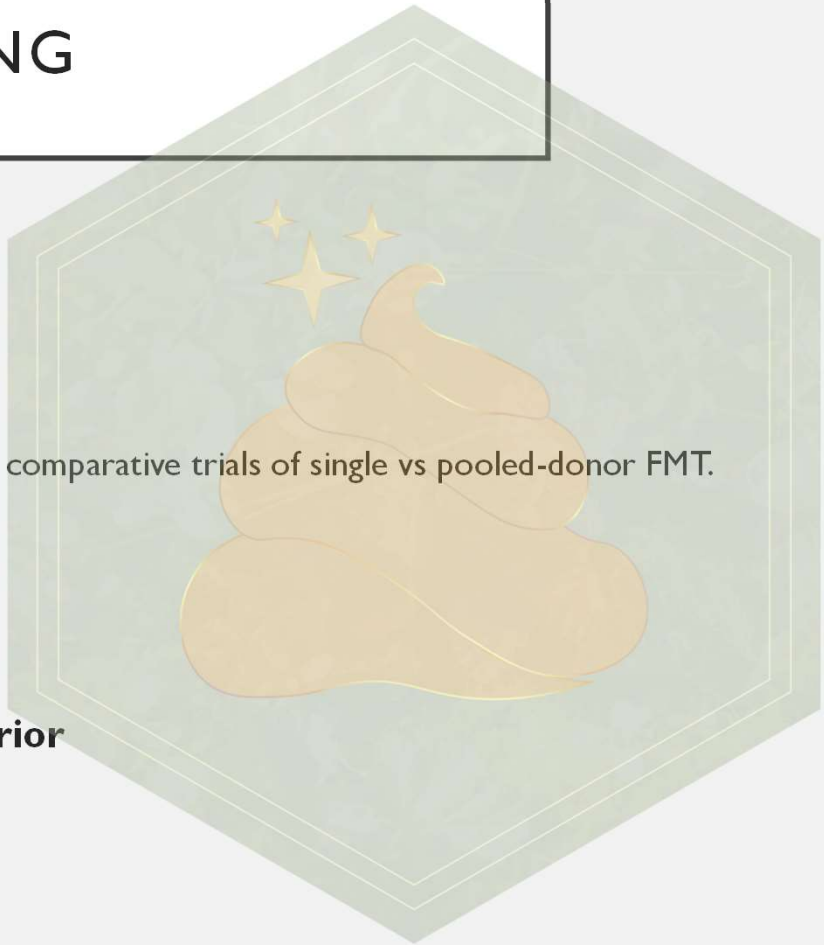
DONORS

- Ideally between the ages of 18 and 60:
  - Donors outside these age groups have been excluded from all RCTs
  - Donors > 60 years have losses in the phylum Actinobacteria and family Bifidobactericeae

- Ideally donors should have normal BMI:
  - 1 case report of weight gain in recipient of FMT from an overweight donor, but this has not been replicated elsewhere in the literature.
  - Some RCTs have excluded donors without a 'normal' BMI.

PROCESSING

- **Use >50g stool**
  - Systematic review: ~4-fold increase in recurrence if <50g used
- **Single donor fine**
  - Overwhelming majority of studies have used single donors. No comparative trials of single vs pooled-donor FMT.
- **Dilute the stool 1:5 with normal saline**
  - This reflects the protocol in the majority of studies.
- **Process the stool within 6 hours.**
- **Can be frozen (with glyercol added) also – non-inferior**
  - But use stool within 6 hours of thawing.



WHERE TO GET THE STOOL FROM?

- Case series have used family members – easier to get stool from for free!
- No evidence this works better than unrelated donors though.
- May be riskier too
- Best is probably sourcing from a centralised **stool bank**
  - Standardised testing
  - Rigorous inclusion/exclusion criteria
  - Better monitoring and traceability

ADJUNCTIVE MEDICATIONS TO USE

Upper GI route

- PPI
- Prokinetic

Lower GI route

- Bowel purgative
- Loperamide (single dose)

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0

NEJM 2013;368:407-15

SIDE-EFFECTS

Minor GI side-effects are frequent but transient (usually just first day or so):

- Abdominal discomfort, flatulence, self-limiting irregular bowel movements, constipation, constitutional symptoms

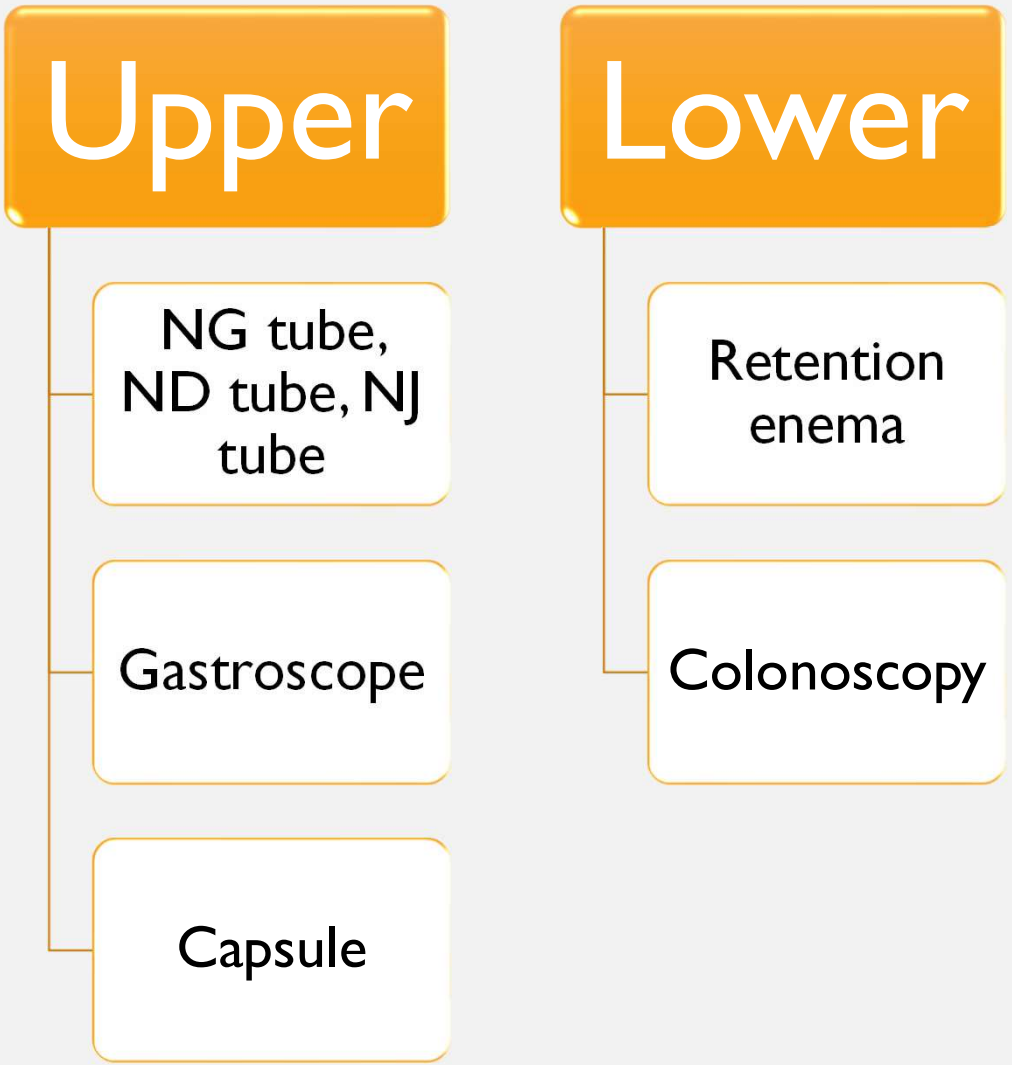
ANTIBIOTICS

DON'T

Give antibiotics within 24 hrs before FMT, or non-CDI abx for 8 wks after FMT.

DO

Give anti-CDI tx for ≥72 hrs prior to FMT (but stop ≥24 hrs before)


Upper
NG tube, ND tube, NJ tube
Gastroscope
Capsule
Lower
Retention enema
Colonoscopy

CHOOSING THE ROUTE

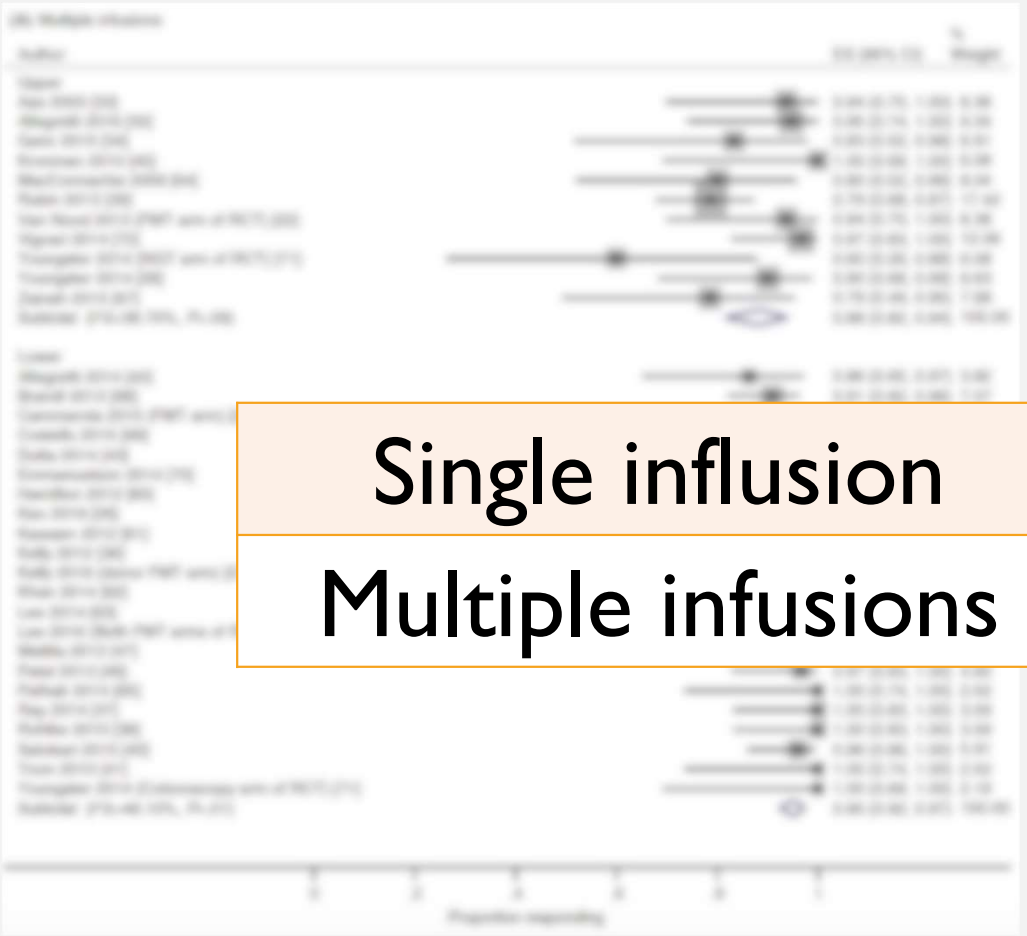
- One small RCT compared NGT vs colonoscopy[1]: resolution of diarrhoea with single FMT in 6/10 via NGT vs 8/10 via colonoscopy.
- In general, seems to be a slight advantage to administering colonoscopically
  - But possible confounders: larger volumes, 'higher concentration' with lower GI administration.

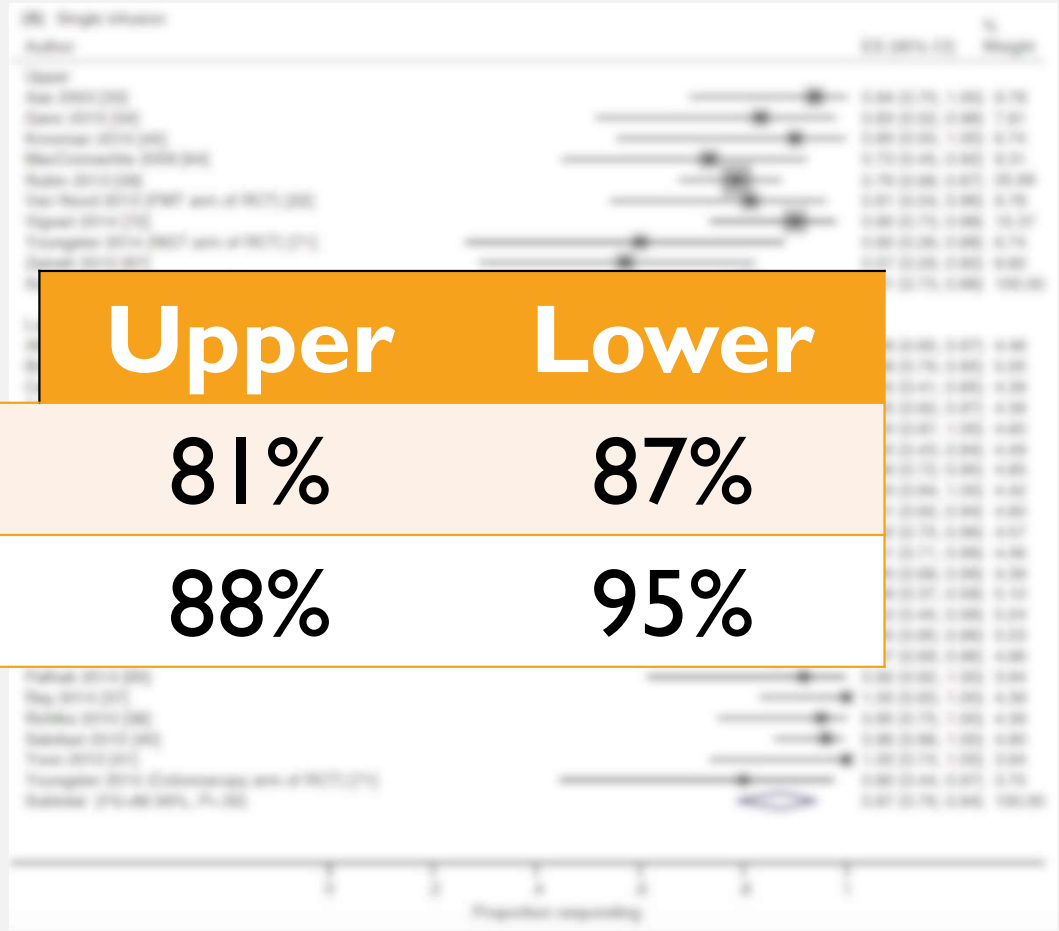
1. Clin Infect Dis. 2014;58:1515-1522.

IS THERE ANY POINT GIVING FURTHER FMT IF INITIAL FMT FAILS?

- YES – seems to work for both initial failures or early relapses.

- Variety of strategies have worked well:
  - Repeat FMT every 24-72 hours until clinical response, or
  - Repeat FMT every 3 days until resolution of pseudomembranes, or
  - Restart vanco x5 days if clinical failure, then repeat FMT





	Upper	Lower
Single influsion	81%	87%
Multiple infusions	88%	95%

AND THE CAPSULE?

116 patients randomized to capsule vs colonoscopy

96% of both groups responded and remained free of *C. diff* at 12 weeks

JAMA | Original Investigation

Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection

A Randomized Clinical Trial

Dina Kao, MD, FRCPC; Brandi Roach, RN; Marisela Silva, MD; Paul Beck, MD, PhD, FRCPC; Kevin Rioux, MD, PhD, FRCPC; Gilaad G. Kaplan, MD, FRCPC; Hsiu-Ju Chang, MSc; Stephanie Coward, MSc; Karen J. Goodman, PhD; Huiping Xu, PhD; Karen Madsen, PhD; Andrew Mason, MBBS; Gane Ka-Shu Wong, PhD; Juan Jovel, PhD; Jordan Patterson, MSc; Thomas Louie, MD, FRCPC

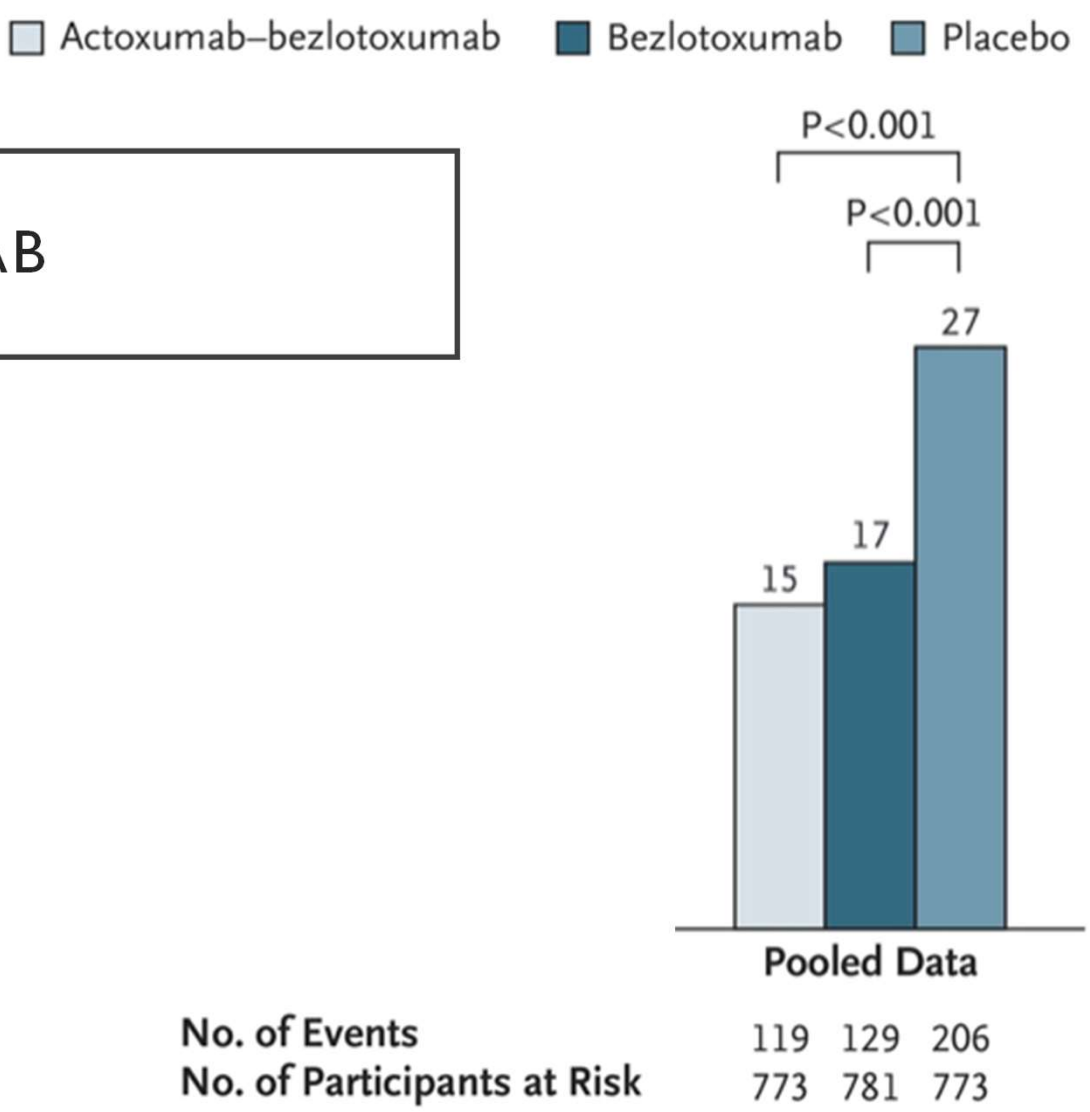
BUT

1. Capsules are big
2. Regimen often requires swallowing 30-40 tablets in a short period

JAMA. 2017;318(20):1985–1993

BEZLOTUXUMAB

- Monoclonal antibody that binds to and neutralizes C. diff toxin B.
  - Prevents toxin B from attaching to colonic cells → averts further inflammation.
- Given as a single intravenous dose (10 mg/kg).
- <u>Doesn't kill the organism – needs to be given with conventional treatment.</u>



SUMMARY – WHAT'S NEW

- Consider vancomycin upfront for all C. difficile infections.
  - Metronidazole is acceptable for non-severe cases.
- For first relapse, use vancomycin taper (or fidaxomicin if you can get it)
- For subsequent relapses, use FMT.
- Bezlotoxumab works as an adjunct to prevent relapses, but only moderately so, and it's expensive (and not available here anyway!)